PATENT
Attorney Docket No.: A-67984/464334-00102/RFT/TAL/THR

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Chang *et al.*

Serial No.: 09/500,376

Filed: February 8, 2000

For: *Baculovirus Produced Plasmodium Falciparum Vaccine*

Group No. 1645

Examiner: A. Navarro

CERTIFICATE OF MAILING
I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Mail Stop RCE Commissioner for Patents, P. O. Box 1450, Alexandria, Virginia 22313-1450 on:

Date: Dec. 17, 2003

Signature Traci Ropp
Traci Ropp

DECLARATION OF SANDRA P. CHANG PURSUANT TO 37 CFR§ 1.132

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

The undersigned, Sandra P. Chang, hereby declares as follows:

1. I received a Ph.D. degree in 1983 from Oregon Health Sciences University. I currently hold the position of Professor of Tropical Medicine and Medical Microbiology, John A. Burns School of Medicine, at the University of Hawaii at Manoa.

2. Attached to this Declaration as Exhibit 1 is a copy of my curriculum vitae and a list of publications.

3. I am the co-inventor of several patents in the field of *Plasmodium Falciparum* vaccines, including U.S. Patent Nos. 6,420,523, 6,214,353 and 5,756,101.

4. I am a co-inventor of the above-identified patent application and I have read and I understand the patent application.

5. I have read the Office Action issued on June 18, 2003 in the present patent application. I understand that the Examiner is concerned about the diversity of the species claimed in the application, and that it is the Examiner's position that the species disclosed in the specification are too few and too diverse to sufficiently describe the claimed genus. I disagree with this position.

6. The genus of *Plasmodium falciparum* gp195 alleles (and hence corresponding p42 polypeptides) is simply not as large as the Examiner seems to think. For example, the C-terminus of the merozite surface protein (gp195) from 15 different isolates of *Plasmodium falciparum* from Africa, Asian and Latin America possess only a few nucleotide changes leading to amino acid alterations at only four positions out of 102 residues. (Kang and Long , *Mol. and Biochem. Parasit.* 73 (1995) 103-110.) Similarly, gp195 alleles in 60 isolates from Brazil and 37 from Vietnam, possess only five single nucleotide polymorphisms in block 17 (a 19 kDa region at the C-terminus). (Ferreira et al, *Gene* 304 (2003) 65-75.) Additionally, there are only two known gp195 alleles. (Kang and Long , *Mol. and Biochem. Parasit.* 73 (1995) 103-110.)

7. We have evaluated p42 polypeptides from 4 different isolates of *Plasmodium falciparum* designated FUP, MAD, WEL and K1. These p42 polypeptides are processing fragments of a gp195 surface glycoprotein from the different *Plasmodium falciparum* isolates. Members of the isolates represent both of the two known gp195 alleles. The first allele, designated the MAD allele, is represented by the p42 polypeptides isolated from the FUP and MAD isolates. The second allele, designated the Wellcome-K1 allele, is represented by the p42 polypeptides isolated from Wellcome and K1 isolates. These isolates show high homology as between the specific alleles : there is 98% homology between the FUP and MAD isolates and 97% homology between the Wellcome and K1 isolates. In addition, Southern blot hybridization using probes for the two alleles revealed that FUP and three other isolates designated Pf857, FVO and Hond-1 were characterized as having either the MAD allele or the K1 allele. This data illustrates the highly homologous nature of the disclosed p42 polypeptides.

8. I also disagree with the Examiner's suggestion that the very limited inter-species variation noted above will drastically alter the functionality of the polypeptides. The Examiner mentions the fact that sickle cell anemia is caused by single amino acid substitution in hemoglobin. This single substitution results in hemoglobin that tends to cluster together and

form long rods illustrating the strong structure:function relationship in heme proteins. The Examiner refers to functional attributes of polypeptides only in the sense of a catalytic or enzymatic activity. However, this viewpoint is not applicable to our use of the p42 polypeptides, which derive their functionality by inducing an immune response As shown by our data in the specification, the p42 polypeptides from the isolates each elicit antibodies that are cross-reactive with other p42 polypeptides. This cross-reactivity allows the antibodies to be functionally effective against various *Plasmodium falciparum* infections.

In addition, hydropathy studies show that, despite variation in primary structure, there is a conservation of three-dimensional structure as between the gp195 proteins from the various *Plasmodium falciparum* isolates. (See, Chang, et al., "Plasmodium falciparum: Gene Structure and Hydropathy Profile of the Major Merozoite Surface Antigen (gp195) of the Uganda-Palo Alto Isolate" *Experimental Parasitology*, 67: 1-11 at pages 5-6 (1988)) Such structural conservation, in view of the cross-reactivity between antibodies, suggests that the ability of the gp195 proteins to induce an effective immune response against a *Plasmodium falciparum* infection is more dependent on the overall conformation of the polypeptides than on the primary sequence. As such, one would not expect that one or even several amino acid changes in the p42 polypeptides would affect their ability to induce an effective immune response.

9. I hereby declare that all statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: December 16, 2003

Sandra P. Chang, Ph.D

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